REMARKS

Applicants submit the present Amendment in response to the Office Action mailed November 19, 2003. Claims 1, 2, 4-8, 10, 11, 13-15, 17-21, 23 and 26 are currently pending and under consideration. By this amendment, claims 6-8, 10 and 11 are canceled. This amendment is not to be construed as acquiescence to any basis of rejection and is made without prejudice to prosecution of any subject matter modified by the amendment in a related divisional, continuation, or continuation-in-part application. Favorable consideration of the instant application is requested in light of the amendment and remarks provided herein.

Withdrawal of Previous Rejections

As an initial matter, Applicants would like to thank the Examiner for his reconsideration and withdrawal of the previous rejections under 35 U.S.C. §§ 103(a) and 112, second paragraph, in light of the Amendment and Declaration of Sean Semple, M.Sc. submitted October 7, 2003.

Double Patenting Rejection

The Examiner has maintained his rejection of claims 1-11 under the judicially created doctrine of obviousness-type double-patenting as unpatentable over claims 32-35, 37, 39-57 and 60-63 of co-pending Application No. 09/896,812. In addition, the Examiner indicates in the Office Action mailed November 19, 2003 that claims 1, 2, 4-8, 10, 11 and 23 stand provisionally rejected for the same reason.

While Applicants do not understand the basis for the discrepancy between the claims subject to the maintained rejection and those subject to the new rejection, Applicants request that the Examiner hold this rejection in abeyance until allowable subject matter has been identified.

Rejection Under 35 U.S.C. § 102(b)

Claims 6 and 7 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Madden *et al.*, Proc. Of ASCO, 17: abstract #754 (1998). Specifically, the Examiner asserts that Madden *et al.* teaches a liposomal topotecan formulation wherein topotecan is trapped in the aqueous interior of the carrier and wherein 24 hours after injection, the topotecan remaining in the circulating carriers is almost 90% lactone. The Examiner asserts that this liposomal formulation is the same as the liposomal formulation of claims 6 and 7.

Without acquiescence to this basis and solely to expedite prosecution of the instant application, claims 6 and 7 are canceled by the present amendment. Accordingly, Applicants respectfully request that the Examiner withdraw this basis of rejection.

Rejection Under 35 U.S.C. § 103

Claims 1, 2, 4, 5 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Madden *et al.* The Examiner asserts that Madden *et al.* teaches a liposomal topotecan formulation comprising a lipid, topotecan, sphingomyelin and cholesterol. The Examiner further asserts that the instant claims, even though they recite specific dosages, are obvious in light of this reference, since it is not inventive to discover optimum or workable ranges by routine experimentation.

Claims 1, 2, 4, 5, 13-15, 17-21, 23 and 26 stand similarly rejected under 35 U.S.C. § 103(a) as being unpatentable over Madden *et al.* in view of Ormrod *et al.* The Examiner alleges that, in addition to the teachings of Madden *et al.* described above, Madden *et al.* also teaches that camptothecins have shown good anticancer activity and specifically tests liposomal encapsulated topotecan formulations comprising a lipid, topotecan, sphingomyelin and cholesterol on murine leukemia and melanoma cell lines, including administering multiple doses of the formulation on days 1, 5 and 9. However, the Examiner concedes that Madden *et al.* fails to teach the treatment of the specific cancers recited in claims 13-15, 17-21 and 26 and the amounts of topotecan recited in claims 1 and 17. Rather, the Examiner asserts that Ormrod *et al.* teaches that topotecan has antitumor activity against small cell lung cancer and ovarian cancer and describes dosages within the claimed range. The Examiner concludes that it would have

been obvious to one having ordinary skill in the art to have modified the liposomal formulation and method of using said formulation as taught by Madden *et al.* by using the dosage amounts and dosage schedule as taught by Omrod *et al.* for the treatment of ovarian and small cell lung cancer.

Applicants traverse this basis of rejection and submit that the claimed liposomal topotecan unit dosage forms (claims 1, 2, 4, 5 and 23) and methods related to the same (claims 13-15, 17-21 and 26) are not obvious in light of Madden *et al.*, either alone or in combination with Ormrod *et al.* As an initial matter, Applicants note that the instant invention is based upon the surprising discovery that the claimed liposomal camptothecin formulations demonstrate increased efficacy at equivalent dosages and are efficacious at lower dosages than previously described liposomal camptothecin formulations, as detailed in the previously submitted Declaration of Sean Semple, M.Sc. Thus, the claimed liposomal camptothecin unit dosage forms offer the advantage that they may be administered at lower dosages, resulting in reduced side-effects. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, since neither Madden *et al.* nor Ormod *et al.* teach or suggest the use of liposomal camptothecins within the claimed dosages and, furthermore, the cited references, either alone or in combination, would not motivate the skilled artisan to utilize such lower dosages.

The instant claims are drawn to liposomal topotecan unit dosage forms comprising a topotecan dosage of from about 0.01 mg/M^2 to about 7.5 mg/M^2, which corresponds to about 0.0033 mg/kg to about 2.5 mg/kg. In contrast, the dosages described in Madden *et al.* are substantially higher, ranging from 4.0 mg/kg to 20 mg/kg. Clearly, therefore, Madden *et al.* fails to teach or suggest the claimed liposomal camptothecin dosages. In addition, the Examiner has provided no basis for his assertion that the claimed dosages are obvious in light of Madden *et al.* Indeed, the skilled artisan would have absolutely no motivation to use liposomal topotecan formulations at the claimed dosages in light of the teachings of Madden *et al.* and the general understanding and knowledge in the art. In fact, the teachings of Madden *et al.*, combined with the knowledge in the art, as exemplified by Slater *et al* (which is also cited by the Examiner), actually teach away form the claimed dosages. Madden *et al.* demonstrates the efficacy of dosages ranging from 4.0 mg/kg to 20 mg/kg, which is generally in accordance with

the dosage ranges previously shown to be efficacious using other liposomal camptothecin formulations. For example, Slater *et al.* teaches that dosages of 5 mg/kg and 8 mg/kg both resulted in tumor remission in 10/12 HT-29 xenograft tumor model animals tested, while a dosage of 2 mg/kg resulted in complete remission in only one animal and partial remission in only two animals of the twelve tested (Table 6). Accordingly, the skilled artisan would conclude, based upon Madden *et al.* and the general knowledge in the filed, as exemplified by Slater *et al.*, that dosages greater than 2 mg/kg of liposomal topotecan are required for efficacy. Thus, the claimed dosage ranges, which are much lower than those previously shown to be required for efficacy, would clearly not be obvious in light of Madden *et al.*

Similarly, the skilled artisan would not be motivated by the combination of Madden *et al.* and Ormrod *et al.* to achieve the claimed liposomal topotecan unit dosage forms and methods of using the same. The Examiner's argument that the claimed invention is obvious in light of Madden *et al.* in combination with Ormrod *et al.* appears to rest solely on the premise that the dosages of free topotecan described in Ormrod *et al.* would also be applicable to liposomal topotecan, since it is clear that neither reference explicitly teaches the claimed liposomal unit dosage forms. However, as the skilled artisan would certainly appreciate, it is entirely inappropriate to conclude that dosages efficacious for free topotecan would also be efficacious or optimal for liposome-encapsulated topotecan, as the two compositions have drastically different pharmacokinetic characteristics. As described in the instant application, the claimed liposomal topotecan formulations exhibit elevated and extended plasma drug levels, selective drug delivery to tumor sites, and sustained levels of the active lactone species, as compared to free topotecan. Thus, the skilled artisan would understand that these different characteristics almost certainly directly translate into different optimal dosages for free versus liposome-encapsulated topotecan. Indeed, the previously submitted Declaration of Sean Semple, M.Sc. explicitly recites that the claimed liposomal compositions exhibited increased efficacy as compared to free topotecan at similar dosages. In addition, the Declaration indicates that the claimed liposomal compositions exhibited efficacy at dosages not previously shown to be efficacious using free topotecan (paragraphs 3-6). Accordingly, the skilled artisan would certainly not be motivated to modify the teachings of Madden *et al.*, in light of the specific free

topotecan dosages taught in Ormrod *et al.* to achieve the claimed liposomal topotecan unit dosage form, or methods related to the same. The mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g., In re Mills,* 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch,* 23 USPQ2d 1780 (Fed. Cir. 1992)). At the very most, this combination of references could support only an "obvious to try" argument, which has explicitly been held as insufficient to support a rejection under Section 103. *In re O'Farrell,* 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir.1988).

Claims 8, 10 and 11 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Madden *et al.* in view of Slater *et al.* More specifically, the Examiner indicates that while Madden *et al.* provides the teachings described above, this reference fails to teach the divalent cation ionophore of instant claim 8. The Examiner asserts that Slater *et al.* discloses liposome-entrapped topoisomerase inhibitors including topotecan and also teaches that a gradient can be produced by including a selected ionophore in the liposomes. The Examiner concludes that it would have been obvious to one having ordinary skill in the art to have modified the liposomal formulation of Madden *et al.* by including a selected ionophore to create a pH gradient because of the reasonable expectation of developing a liposome formulation that would be able to load high drug concentrations.

Without acquiescence, claims 8, 10 and 11 are canceled by the present amendment, thereby obviating this basis of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

In view of the above amendments and remarks, Applicants respectfully request allowance of claims 1, 2, 4, 5, 13-15, 17-21, 23, and 26. A good faith effort has been made to place this application in condition for allowance. However, should any further issue require attention, the Examiner is requested to contact the undersigned at (206) 622-4900.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

Carol D. Laherty, Ph.D.
Registration No. 51,909

CDL:jto

Enclosure:
Postcard

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

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